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June 28, 1996

TOWNSEND and TOWNSEND and CREW LLP

By L. Dallara

PATENT

Attorney Docket No. 016243-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:	
Richard H. Tullis	Examiner: J. Martinell
Serial No.: 08/078,768	Art Unit: 1804
Filed: June 16, 1993	COMMUNICATION REGARDING REPLY TO EXAMINER'S ANSWER
For: OLIGONUCLEOTIDE THERAPEUTIC AGENT AND METHODS OF MAKING SAME	

Before the Board of Patent Appeals and Interferences
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Enclosed are three copies of a Reply to Examiner's Answer. The Examiner's Answer was mailed on April 30, 1996, and expressly identified new grounds for rejection.

This Reply is filed within the two-month period alloted under Rule 193 (b). No fee is thought necessary. However, if a fee is required, the Commissioner is authorized to charge Deposit Account No. 20-1430 any fees appropriate to this Communication.

Also enclosed are three copies of a Request for Oral Hearing.

Respectfully submitted,

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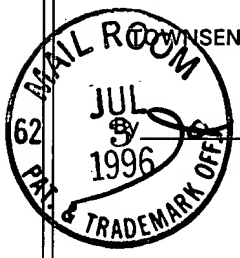

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PATENT

Attorney Docket No. 016243-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Before the Board of Patent Appeals and Interferences
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a Reply to the Examiner's Answer mailed on April 30, 1996. In accordance with Rule 193, the remarks presented below are confined to the new points of argument and to the new ground for rejection.

OK TO ENTER
9/3/96

A. NEW POINTS OF ARGUMENT.

Appellant has identified five new points of argument. The new points of argument are presented in the order found in the Examiner's Answer.

1. Item 2 in Appellant's Issues section is incorr ct.

The Examiner's states on page 3 of his Answer that item 2 of the Appellant's Issues section of the opening Brief is incorrect. Item 2 calls attention to the failure of the Examiner to set forth scientific reasons for his enablement

rejection as it relates to the sufficiency of the application to teach those of skill which stabilized oliogonucleotides are of use in the invention. The text of item 2 is as follows:

2. Can an Examiner reject claim 71 as non-enabled because he believes, without objective reasons, that those of skill might have to conduct a literature search to identify other members of the family of stabilized nucleic acid and in view of the fact that the family was summarized in the literature by a routineer three years before the filing date of the parent application?

The Examiner improperly interprets this item as requiring the Examiner to set forth objective reasons solely because he believes a literature search is needed. The Examiner then states that item 2 is incorrect because he has objective reasons for believing that one of skill might need to perform a literature search to identify stabilized oligonucleotides.

The logical inconsistency being applied here is known as the "Fallacy of Irrelevant Truth." The Examiner confuses the true issue by improperly focusing the reader's attention on an irrelevant truth while in fact he is ignoring the true issue in dispute.

It is Appellant's position that item 2 properly sets forth the legal impropriety relating to one of the Examiner's two bases for rejecting claim 71. Throughout the prosecution, Appellant has tried to have the Examiner clearly articulate his bases for his §112 rejection along with objective reasons. Appellant would then challenge those objective reasons or concede the position as well taken.

The Examiner now asserts that item 2 is incorrect because he "has objective reasons to believe a literature search might be needed." This was never a basis for the §112 rejection. Item 2 is simply setting forth one of the subissues surrounding the enablement rejection, i.e., what reasons does the Examiner have for believing a literature search was so beyond the skills of ordinary nucleic acid chemists that the search constituted undue experimentation under the *Forman* factors? Clearly, item 2 is referring to a failure of the Examiner to respond objectively to the fact that one of skill might have to conduct a literature search

and to the fact that the literature was not only available but summarized in an article relating to antisense technology (against virus infections) at least three years before the 1981 filing date. To isolate one of the conjunctive clauses in item 2 and declare the entire item incorrect is misleading.

More specifically, the Board's attention is directed to paper 32 where the Examiner states that:

> There is not enough direction in the application as filed to lead one of skill to use any stabilized oligo or to search the literature to find same.

Thus, it should be clear that the concern raised by the Examiner was not whether a literature search was necessary, but whether the specification adequately informed those of skill by virtue of its generic description and its single example to identify other stabilized oligonucleotides.

In response to this criticism of the specification, the Appellant presented declarations from Drs. Schwartz and Ruth stating that those of skill are highly trained persons with Ph.D.s; that these persons would have known the stabilized oligonucleotides in question; that even if one did not know of such oligonucleotides, they could be identified in a routine literature search; and, that the Summerton 1978 reference reviewing this work was proof that a routineer was able to identify this very body of knowledge at least three years prior to Appellant's effective filing date.

Appellant has repeatedly requested a substantive response to these several objective reasons which are summarized on page 14 of the Brief. No substantive response has ever been provided with objective reasons rebutting the declarants' statements of fact. The Examiner's rebuttal has been limited to restating his grounds for rejection, and now to misstating the grounds for rejection. The true issue is whether the Examiner has objective grounds to believe that a literature search might require undue experimentation in view of the specification? The misstated issue is whether there is objective reason to believe that a literature search might be required?

The later basis for rejection has never been at issue and has no authority at law. In fact, it presumes a improper point of law. The Examiner

would have the Board affirm his rejection under a *per se* rule. The rule would require that any time a literature search is required to identify all members of a family of elements, it is *per se* undue experimentation and is an irrebuttal legal conclusion. This is clearly wrong. Accordingly, the Board is asked to reject this position and reverse the rejection of claim 71.

2. What is the meaning of colorable?

The Examiner is confused by the Appellant's use of the word "colorable" in item 3 of the Issues section. The Examiner makes reference to this word on pages 3 and 14 of the Answer. Appellant is using the term in its ordinary sense. It means "seemingly valid or genuine." The issue is important because it focuses attention on an inconsistent position of the Examiner.

The inconsistency relates to the second of the two bases used by the Examiner to maintain the §§112 rejection. Appellant respectfully submits that when the Examiner asserts that the specification is insufficient to teach "which" stabilized forms of oligonucleotides can be used in the invention, he raises two questions.[1] First, whether one of skill would know which stabilized oligonucleotides are being referred to by the applicant, and, second, whether they would work in the invention without undue experimentation.

Appellant urges that the first basis is not a colorable basis for the §112 rejection in view of the prior art of Summerton which summarized the relevant literature relating to stabilized oligonucleotides several years before Appellant's effective filing date and the two declararants' statements detailed in the Brief at pages 9-13.[2] Yet, the Examiner never clearly withdrew this first basis

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[1] See page 15 of the Answer where the Examiner states that "This lengthy argument cannot be convincing in the absence of even a mention of <u>which</u> oligonucleotides to use."

[2] In addition to the inventor's preferred stabilized oligonucleotides, other stabilized oligonucleotides available in 1981 were thio-substituted, alkyl phosphonates and methylated oligonucleotides. These stabilized oligonucleotides were set forth on page 5 of the Response filed on July 14, 1995, and evidenced by references predating the effective date of the application, and by two Rule 132 declarations.

for the §112 rejection.

Appellant believes that the reason this first basis was not expressly withdrawn is that withdrawal would focus all the attention on the inconsistent nature of the second basis for rejection. The inconsistency is subtle and involves a related patent with claims directed to phosphotriesters.

The Board's attention is directed to related case, US Pat. No. 5,023,243. This patent, having the identical specification as the application now before the Board, was deemed sufficiently "enabled" to issue method claims to Dr. Tullis for inhibiting protein synthesis using phosphotriester-stabilized oligonucleotides. The claims were issued without proof of clinical success. Now, however, this same specification fails to enable other stabilized oligonucleotides--not simply for failing to expressly set them forth, but for substantive reasons, i.e., no proof of *in vivo* operability absent undue experimentation.

Accordingly, the later basis for rejection is inconsistent with the issuance of U.S. Pat. 5,023,243, and Appellant respectfully submits that the Examiner is unwilling to withdraw the first basis of rejection, although he has no objective reasoning to support it. If the Examiner were to concede that his first basis for the enablement rejection is not proper, he would have to admit the patentability of claim 71, which is limited to stabilized oligonucleotides, for the same reasons that US Pat. No. 5,023,243 issued. Thus, the Appellant argues that the first basis of rejection, limited to how difficult it would be to actually identify the other members of the group of stabilized oligonucleotides, is not colorable or seemingly genuine. It would only become colorable if the Examiner had identified objective reasons why he believed the physical identification of the other stabilized oligonucleotides would have required undue experimentation.

In contrast, the second basis for the enablement rejection is thought "colorable" because it is supported by reasonable questions to which the examiner is entitled to substantive answers -

Will stabilized oligonucleotides bind to mRNA without undue experimentation?

Will stabilized oligonucleotides enter cells without undue experimentation?

Accordingly, method claims embracing the genus of oliogonucleotides would be allowable presuming Appellant convinces the Board that unstabilized and stabilized oliogonucleotides will generally work in the invention. Subsections VI.3 and VI.4 of Appellant's Brief are directed to substantively answering these two questions.

3. Review of Post filing date references, Exhibits A-E.

At page 7, the Examiner presents an argument that appears to misrepresent the Appellant's Brief. The Examiner, at page 7, argues for the first time that Appellant's arguments on pages 6-21 are unconvincing, not upon their own merits; but, because Exhibits A-E were improperly presented in 1992.

Nowhere in Appellant's Brief is there any mention of these five references. Appellant's present attorney took over prosecution in 1994. A continuation application was filed, and a new set of claims were added by way of a preliminary amendment. The amendment and subsequent legal argument overcame a 14 year old obviousness rejection, and Appellant's attorney has challenged the sole remaining rejection under §112 by presenting multiple arguments supported by new references and new Rule 132 declarations. The 1992 Exhibits A-E have not been relied upon since they were originally presented. The Appellant is not seeking to have the Board consider references A-E as controlling of patentability.

4. Point 6 on page five of the Response filed July 20, 1995, is not an objective reason.

The Examiner concludes his summary of this particularly complex prosecution history by focusing the Board's attention on a irrelevant counting error by Appellant's attorney. This error was not continued in the Brief and is newly raised in the Answer. The Appellant's declarants identified five objective reasons why they believed that one of skill in 1981 would have understood the specification, as filed, to include modified oligonucleotides other than

phosphorothioesters and that those of skill would either have known of these analogues or have been readily able to identify them. Based upon these five reasons, the declarants offered their considered opinion.

In the prosecution papers that followed, the Appellant complained that these five objective reasons and conclusion had been summarily dismissed by the Examiner without substantive rebuttal. During that discussion, Appellant's attorney included the conclusion as one of the objective reasons and counted six objective reasons on page 5 of the Response filed on July 20, 1995. Appellant regrets the counting error, but he fails to see why this error excuses the Examiner from substantively responding to the five objective reasons.

Those five objective reasons are condensed in Appellant's Brief into three objective reasons at Section 1B on page 11. The Examiner's entire response can be found on page 15 of the Answer where the Examiner states:

> Section 1B of the brief (pages 9-13) is not convincing for reasons given above in connection with the declarations of Drs. Schwartz and Ruth and in connection with the discussions of each of the references submitted as evidence in conjunction with those declarations.

Appellant simply fails to find any substantive objections in the Answer, nor in the prosecution history, and invites the Board to find and identify them. The fact is that at least four stabilized oligonucleotides were known in 1981.[3] Those chemists of skill in nucleic acids, for the reasons set forth in the Brief on page 11, would have known of these nucleic acid analogs, and those of lesser skill would have been able to identify them by a simple literature search.

5. The Inventor has not provided a declaration.

The Examiner, for the first time, impliedly questions the failure of inventor, Dr. Tullis, to provide a declaration. The Examiner writes on page 18:

> We have not heard from the inventor about this since and there is no evidence in the record that the inventor's own statements were incorrect.

The Examiner has not previously asked for a declaration from the inventor.

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[3] See footnote 2, supra.

Appellant has several responses. Appellant's attorney believes the inventor's statements in both the file history and in the 1992 Biotechnology International article to be clearly taken out of context. The meaning of both statements is crystal clear when you view them in their context. The Brief substantively addresses both these statements at Section 5(c) of the Brief. Even if these two statements were properly taken as ambiguous with regard to their meaning, the interpretation taken by the Examiner is patently wrong when viewed under objective, scientific criteria. In view of the clarity of the text of both statements, a declaration from Dr. Tullis was not considered necessary. In addition, the inventor is no longer readily available due to a change in his employment. He no longer works for the assignee, Molecular Biosystems.

Furthermore, the statements at issue were not deemed to be sufficiently problematic that expert declaratory evidence was needed to interpret the statements. While the undersigned attorney considered having the two experts, Drs. Schwartz and Ruth, provide declaratory evidence as to how one of skill would interpret the statements in dispute, it was ultimately decided that there was no need for expert interpretation. The Examiner is stretching the intent of the statements well beyond their context. Black is black. The full text of the documents speak for themselves and additional declarations are not necessary. This being stated, had the Examiner asked for a Rule 132 declaration on this point, one would have been requested from Dr. Tullis and from anyone else competent to read and understand the statements and their context.

B. NEW GROUNDS FOR REJECTION.

The Examiner's Answer raises new grounds for rejection. The new grounds for rejection address the sole colorable and substantive basis for rejecting the claims - will unstabilized and stabilized oliogonucleotides generally work in the invention? In support of the Examiner's position that it requires undue experimentation to practice the invention, the Examiner cites two new references, Gura (1995) and Rojanasakul (1996). Appellant has four responses. First, he will urge that these references are not relevant to patentability. They are addressing

difficulties in curing diseases and do not raise a question relevant to the salient issue surrounding the patentability of the claims on appeal, i.e., whether oligonucleotides complementary to the coding region of mRNA will bind to mRNA and specifically downregulate protein expression. Second, Appellant will note that the Examiner readily asserts "later state-of-the-art literature" against the Appellant, but he refuses to consider later state-of-the-art literature when it clearly refutes his position by establishing that unmodified oligonucleotides can inhibit protein expression under *in vivo* conditions. Third, Appellant will present three later state of the art references that establish the viability of using modified oligonucleotides to regulate protein expression even under clinical conditions. Fourth, there is serious question of law raised by the Examiner's reliance on these two new references. The MPEP sanctions the use of new references in an Examiner's Answer under limited situations; but, the Board's opinion in *Ex parte Raske*, 28 USPQ 2d 1304 (1993), is at odds with the Examiner's late use of the two new references for establishing the current state of the art.

1. Gura and Rojanasakul are irrelevant.

The central question before the Board is whether it would require undue experimentation to identify unmodified oliogonucleotides or modified oliogonucleotides that would control expression levels of specific proteins by binding to mRNA in a cell. The Examiner argues that unpredictability surrounding stability of oligonucleotides, cell uptake of oligonucleotides, and binding of oligonucleotides render the generic claims unpatentable because it would require undue experimentation to practice the invention in a clinical setting. In response, the Appellant argues that: (1) clinical success is the the controlling test for patentability of claims not reciting clinical uses; and, (2) both unmodified and stabilized oligonucleotides work under *in vitro* and *in vivo* conditions to a degree adequate to satisfy the patent statute.

The Gura and Rojanasakul references are irrelevant because they address miscellaneous problems the antisense industry is having perfecting the use of therapeutic oligonucleotides for clinical applications. These two articles mention

therapeutic applications that incorporate this invention, which pertains to targeting mRNA with complementary oligonucleotides. The Board should note that the papers, without distinction, also discuss therapeutic applications that involve anti-gene nucleic acids, anti-viral nucleic acids, and ribozyme technology.

The relevant case law could not be clearer. Appellant's invention need not be commercially perfect in order to be patentable. Practicalities surrounding clinical or commercial applications for an invention are not bars to patentability for claims that do not recite therapeutic applications as their basis for patentability.

The pending claims do not recite therapeutic uses. They are directed to the control of expression of specific proteins in a cell. While this invention has clinical applications, these uses were not perfected in 1981. There are plenty of obvious, non-clinical uses for regulating protein expressing. These include agricultural uses to improve crop production, research tools, and antimicrobial application in industrial settings such as fermentation.

The two new references could not be clearer that their collective criticisms are limited to the **degree** of effectiveness relating to all of antisense technology in clinical applications. The references are not critical of the scientifically accepted fact that one can use complementary oligonucleotides to bind to mRNA and selectively inhibit protein expression both under *in vitro* and *in vivo* conditions. In the abstract written by Rojanasakul, he first speaks well of oligonucleotide(ON)-based therapy, and then criticizes it's "effectiveness" to date. He states on page 115 in the abstract:

> ONs have several advantages over traditional drugs, notably their exquisite specificity to target sites and their ease of design. However, their effective use has been limited due to several problems.

The operative word is "effective". In the context of this author's article, the ON is not sufficiently effective enough to provide meaningful therapeutic benefit in every clinical context. Nowhere does the author imply that protein inhibition would not occur to a measurable degree or even to a marginally beneficial degree.

Appellant wishes to direct the Board's attention to a paragraph of Rojanasakul that the Examiner has apparently overlooked. At this paragraph, Rojanasakul expressly supports an important position of the Appellant. As the Board may recall, Appellant has asserted that unmodified oligonucleotides are useful in the invention for *in vivo* applications, but are less desirable than stabilized oligonucleotides due to degradation problems. As explained in the file history, those of skill solve this degradation problem by simply increasing the concentration of unmodified oligonucleotides[4]. On page 119, column 1 of Rojanasakul, the author expressly states:

> However it was soon realized that phosphodiester ONs are easily degraded in cell culture medium containing serum due to 3'-exonuclease digestion [46]. Consequently, the antisense effects could only be observed if high ON concentrations (up to 100 μM) were used [47].

It is unfair of the Examiner to use Rojanasakul for propositions that support his position while ignoring express statements that support Appellant's position. Moreover, when Appellant submitted post filing date references to support this very position, the Examiner steadfastly refused to consider those references substantively because they were published after the effective filing date of the invention.[5]

As with Rojanasakul, the Gura paper limits its criticism to clinical applications. The author's concerns regarding antisense technology is not over whether expression of protein inhibition occurs via the Appellant's invention, but whether clinical uses will pass FDA review in view of side effects and effectiveness. These are not issues properly within the purview of the Patent Office.

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[4] See Section 5 of Argument section of the opening Brief and the Response filed on July 14, 1995, at pages 11-12 describing various references where unmodified oligonucleotides downregulated protein synthesis in a specific manner.

[5] See subsection 5 A of the Argument section of Appellant's opening Brief for details. In particular, see Exhibits 7-9 of Appellant's Response submitted on July 20, 1995.

Moreover, the Gura paper is not a peer reviewed article by a qualified person of skill. It was written by a reporter for the Chicago Tribune.[6] This explains the overly dramatic writing style such as the silly hyperbole on page 575 ... "But do they?" If "they" didn't, the clinical studies listed on page 576 of the Gura article would not be going forward. Appellant objects to the Examiner's reliance upon this type of article for its scientific significance. It is demeaning to the examination process when the words of a lay newspaper reporter are being used to contradict the statements of the declarants who are highly skilled in nucleic acid chemistry and have spent years studying this technology.

Perhaps an analogy will be helpful to conclude this section. If an inventor develops a new method for permanently joining materials using a toxic glue, does he have to proviso out joining human bone because his claims are broad enough to read on orthopedic uses and such uses might require undue experimentation to practice? This is the situation presented by the Examiner. He views the invention exclusively through the foggy glasses of the Food and Drug Administration. Yes, the invention required years of additional development to be effective under clinical conditions, and, yes, the claims embrace all uses including clinical applications; but, the appealed claims are not directed to clinical uses and the invention is not necessarily a clinical use.

Let others receive patents on improvements perfecting the delivery of the oligonucleotides for clinical uses of this invention. Clearly the Examiner's newly cited references teach that such inventions are needed and are forthcoming. But the invention before the Board is based upon the surprising discovery that you can bind a complementary oligonucleotide to mRNA and specifically inhibit protein expression in a living cell. This discovery or insight was contrary to the conventional wisdom in 1981, and the resulting invention has a host of obvious and exciting uses which extend well beyond the human clinical arena.

To deny Dr. Tullis patent protection for his inventive method of downregulating protein simply because he failed to enable the cure for cancer is

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[6] See page 577 of the Gura article.

wrong. It is as wrong as denying an inventor a patent for carrying water in a bucket because the bucket will not function without undue experimentation in the weightless vacuum of the moon.

2. The Gupta and Rojanasakul references are not the only references addressing the clinical potential of the Appellant's invention.

Attached to this Reply are Exhibits 1-3. These exhibits are the results of Appellant's search for recently published articles on antisense technology by reputable scientists in peer reviewed journals. The purpose of presenting these three references as extrinsic evidence is simply to place the Examiner's concerns into their proper context.

The concerns raised by the Examiner are not scientifically meaningless. They are true concerns of clinicians; but, they are not legally adequate to militate against patentability for the pending claims. The three publications attached to this reply should place the issue into better perspective than the references selected by the Examiner.

In Mercola and Cohen, *Cancer Gene Therapy*, 2:47-59 (1995), the authors raise (on page 49) the same concerns as the Examiner and as Rojanasakul with regard to degradation and cell uptake, but conclude that despite these concerns, clinical and other uses have been successful. On page 49, column 1, the authors write:

> Nevertheless, some 36 applications of phosphorothioate nucleotides have been reported, and these represent a considerable body of evidence that antisense is a useful approach for delineation of gene function, apart from its therapeutic potential.

On page 49, column 2, the authors write that clinical studies are underway against five diseases.

The Putnam article in *American J. Health-Syst. Pharm* 53:151-160 (1996), provides a more favorable projection on the future of antisense technology than the Examiner's references. Putman also addresses the same concerns of clinicians; but, he reports in the abstract that "antisense therapeutic agents bind to DNA or RNA sequences, blocking the synthesis of cellular proteins with

unparalleled specificity." Putnam's conclusion on page 158 is particularly optimistic of the clinical applications.

Finally, the Agrawal and Akhtar article in *TibTech* 13:197-199 (1995) is particularly optimistic about the potential of antisense efficacy.

It is Appellant's hope that these three references will place the current state of the clinical art into proper context. In short, and despite concerns, the clinical efforts of antisense technology have been ongoing and fruitful. Clearly, the Examiner has overstated the reality when he writes on pages 14-15 of the Answer that Gura and Rojanasakul are evidence "that undue experimentation would indeed have been necessary because this problem persists nearly 15 years after the effective filing date of the instant claims." For despite these several concerns, the claimed invention is being used in ongoing clinical trials.

The Examiner asserts on page 16 of the Answer that Appellant has made a sweeping generalization when urging that all the oligonucleotides known in 1981 were capable of being taken up by cells. This is not a "sweeping" generalization. The two declarants provided objective support for this generalization by citing to specific references that teach that cells take up the stabilized oligonucleotides[7]. The Examiner urges that the Gura and Rojanasakul references are at odds with this sweeping generalization but does not point to any passage that indicates that the stabilized oligonucleotides do not enter cells. In fact on page 120, Rojanasakul specifically teaches that unmodified, phosphorothioate-modified and methylphosphonate-modified oligonucleotides all enter cells but that the methylphosphonates use a different mechanism from the other two oligonucleotides.

The Examiner is misinterpreting Rojanasakul. He implies that Rojanasakul states that it takes undue experimentation to get modified oligonucleotides into cells, but Rojanasakul, on pages 120-121, only states that they enter cells at different rates. The fact that different analogs enter cells at different rates or through two distinct mechanisms is of no consequence to the

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[7]See pages 16-17 of Appellant's Brief.

patentability of the claims. Moreover, when the cell permeability of phosphothioesters are considered with the Rojanasakul teaching that unmodified, phosphorothioate-modified and methylphosphonate-modified oligonucleotides all enter cells, Appellant's sweeping generalization becomes verified as fact. The Examiner has not identified any stabilized oligonucleotide available in 1981 or later that cannot enter living cells.

The Examiner further asserts that the Gura and Rojanasakul references are at odds with Appellant's position that all stabilized oligonucleotides will bind to mRNA. Again, there is no statement in the references to support the Examiner's position. The two references merely state that the modified oligonucleotides vary in their binding strength. Stabilized oligonucleotides are always designed by chemists to bind to complementary nucleic acid. It is of no importance that they might vary in their relative binding strength (see Rojanasakul at page 119, 2nd col) or that the modified oligonucleotides might get entangled by cell proteins and that higher doses might be needed to see clinical efficacy (see Gura at the paragraph bridging pages 576-577). All that matters is the fact that they all effectively bind and they do effectively down regulate protein synthesis by targeting mRNA. Nothing else is required of the appealed claims under the modern patent law.

3. If the Board considers the post filing references of Gura and Rojanasakul references as extrinsic evidence, it should also consider Appellant's post filing dat references.

The Board's attention is directed to page 25 of the Appellant's Brief where three separate references (Exhibits 7-9 attached to the Rule 132 Declarations of Drs. Schwartz and Ruth mailed April 14, 1995) were presented. These three references describe three independent studies where unmodified oligonucleotides downregulated specific protein expression under *in vivo* conditions by simply injecting the oligonucleotides into the animals.

The Examiner substantively challenged the other Exhibits 1-6, but has steadfastly refused to substantively consider Exhibits 7-9. The sole grounds for not considering these three exhibits are that they were published after the effective

filing date of the subject applications. The Examiner's reasoning is found on page 17 of his answer.

According to the case law, establishing the state of the art at a previous moment in time is only one of several legally acceptable reasons for considering extrinsic evidence. Other reasons include proof that the application was fully enabled as filed, or that what was taught in the application actually works. It is improper for the Examiner to arbitrarily rely on the Rojanasakul art and Gura references for purposes of supporting his own position regarding the state of the art and then deny to the Appellant application of the same principle of law. In his Answer, the Examiner fails to address the legal basis for this arbitrary action. In addition, he ignores Appellant's legal analysis of extrinsic evidence as explained by the CCPA in *In re Hogan and Banks* on page 22 of his Brief.

4. Appellant objects to the Examiner's reliance upon Rojanasakul and Gura at this late phase of prosecution.

The Examiner has cited Rojanasakul and Gura with the apparent authority of MPEP 1208.01. Appellant respectfully asks that the Board review the Examiner's reliance of these two references in view of *Ex parte Raske*, 28 USPQ 2d 1304 (BPA&I 1993). As in the subject case, the examiner in *Raske* cited new art in his Answer to establish the state of the art. The Board chose to ignore the newly cited references as improperly introduced and viewed them as "an improper effort to bring these references in the 'back door'." Accordingly, Appellant requests that the Rojanasakul and Gura references not be considered.

If the Board believes that *Raske* is controlling law, Appellant will concede that Exhibits 1-3, attached herein as rebuttal to Rojanasakul and Gura, are not properly presented and likewise should not be considered.

Respectfully submitted,

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Attachments: Exhibits 1-3

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